Investigation of prognostic factors affecting efficacy in standard chemotherapies as first-line and second-line treatment for advanced non-small cell lung cancer

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Abstract

Platinum-based regimens are recommended as first-line chemotherapy for advanced non-small cell lung cancer (NSCLC), and docetaxel is usually used as second-line chemotherapy. So far, analyses of efficacy outcomes have not yet been systematically performed using large patient cohorts in each of the platinum- and docetaxel-based chemotherapies. The present meta-analysis aims to investigate the prognostic factors affecting overall survival (OS), progression-free survival (PFS) or time to progression (TTP), and overall response rate (ORR) in carboplatin- and paclitaxel-based first-line chemotherapy and docetaxel-based second-line chemotherapy for advanced NSCLC.

A literature search in PubMed for randomized phase II and III clinical trials in patients with NSCLC treated with carboplatin and paclitaxel as first-line chemotherapy and with docetaxel as second-line chemotherapy was performed, and prognostic factors affecting OS, PFS or TTP, and ORR were investigated by regression analysis.

Sixty-one treatment arms in 53 phase II and III clinical trials of carboplatin- and paclitaxel-based treatment and 39 treatment arms in 31 phase II and III clinical trials of docetaxel-based treatment were included in the analyses.

The region of Asia was found to be a prognostic factor contributing to longer OS following treatment with carboplatin and paclitaxel as first-line chemotherapy and docetaxel as second-line chemotherapy. Furthermore, low percentage of performance status (PS) 2 was found to be a prognostic factor of longer OS in patients treated with docetaxel as second-line chemotherapy.

More global clinical trials in patients with NSCLC are expected to be performed across various regions and considering our findings, regional differences between Asian and non-Asian population, including Caucasians, should be considered in the design and interpretation of the

results of global clinical trials of novel agents in patients with advanced NSCLC. Furthermore, the ratio of patients with PS 2 should be considered in the design of global clinical trials of novel agents used in combination with docetaxel as second-line chemotherapy.

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Abbreviations

ALK	anaplastic lymphoma kinase
CI	confidential interval
EGFR	epidermal growth factor receptor
NSCLC	non-small cell lung cancer
OR	odds ratio
ORR	overall response rate
OS	overall survival
PFS	progression free survival
PS	performance status
SE	standard error
TKI	tyrosine kinase inhibitor
TTP	time to progression
VEGFR	vascular endothelial growth factor receptor

1. Introduction

Lung cancer is the leading cause of death related to cancer worldwide, accounting for 12.9% of the 1.8 million total cases of cancer and 19.4% of the 1.59 million deaths in 2012 [1]. Non-small cell lung cancer (NSCLC) accounts for 85% of all cases of lung cancer and approximately 70% of patients with NSCLC present with locally advanced or metastatic disease at the time of diagnosis [2]. The five-year survival rate of NSCLC patients with Stage III and IV disease is 9% and 13%, respectively [3].

First-line chemotherapy for squamous cell carcinoma, adenocarcinoma with mutated epidermal growth factor receptor (EGFR), and anaplastic lymphoma kinase (ALK)-negative type advanced NSCLC are platinum doublet-based chemotherapies, including cisplatin or carboplatin. Cisplatin or carboplatin is used in combination with paclitaxel, docetaxel, gemcitabine, etoposide, vinblastine, vinorelbine, pemetrexed, or albumin-bound paclitaxel. A tyrosine kinase inhibitor (TKI), either erlotinib, afatinib, or gefitinib, is recommended to be added in EGFR-mutation positive patients with NSCLC, and crizotinib is recommended for ALK-positive patients with NSCLC as first-line therapy. Second-line chemotherapy includes docetaxel for patients with NSCLC following treatment with platinum doublet-based chemotherapies [4]. Therefore, to date, both platinum doublet-based chemotherapies as first-line treatment and docetaxel-based chemotherapy as second-line treatment are still the cornerstone of NSCLC treatment.

In recent decades, numerous molecular-targeted drugs have been developed to improve overall survival (OS) through global clinical trials in combination with platinum doublet-based chemotherapies as first-line treatment, such as carboplatin/paclitaxel, cisplatin/gemcitabine, and cisplatin/pemetrexed, and with docetaxel as second-line treatment. Among them, bevacizumab, a vascular endothelial growth factor receptor (VEGFR) inhibitor, demonstrated OS prolongation

in clinical trials in combination with carboplatin and paclitaxel as first-line chemotherapy in patients with NSCLC [5]. Moreover, ramucirumab, a VEGFR inhibitor, demonstrated OS prolongation in clinical trials in combination with docetaxel as second-line chemotherapy in patients with NSCLC [6].

Outcomes of global clinical trials represent data from patients with different background, including quite a few regions and countries. The differences in patient background may influence treatment efficacy in terms of overall response rate (ORR), progression-free survival (PFS)/time to progression (TTP), and OS in global clinical trials that are usually conducted by applying add-on regimens to standard chemotherapies. These differences may complicate the interpretation of the results. Therefore, it is very important to comprehend prognostic factors influencing the efficacy of standard chemotherapies in advance. Such understanding will bring clinical trials on advanced NSCLC to successful results and provide appropriate consideration and evaluation of the results of clinical trials on advanced NSCLC.

Using a meta-analysis, Soo et al. reported that median OS and ORR in Asian and Caucasian trials of platinum doublet-based chemotherapies as first-line therapy significantly differed [7]. Using a meta-analysis of the individual data from nine randomized trials of second-line chemotherapy, Di Maio et al. reported that gender, performance status (PS), tumor histology, disease stage, type of previous treatment, and response to first-line therapy were factors significantly associated with OS [8]. However, analyses of efficacy outcomes have not yet been systematically performed using large patient cohorts for each of the platinum doublet-based chemotherapies as first-line treatment and docetaxel as second-line treatment widely used in global clinical trials.

In this meta-analysis, I first investigated factors associated with OS, PFS/TTP, and ORR in patients with advanced-stage NSCLC treated with carboplatin and paclitaxel as first-line

chemotherapy and docetaxel as second-line chemotherapy. Second, the association between prognostic factors affecting ORR, PFS, and OS was assessed in terms of continuity of clinical endpoints for carboplatin- and paclitaxel-based chemotherapy and for docetaxel-based chemotherapy, respectively. Third, I assessed the association of prognostic factors of first- and second-line treatments in terms of continuity of medical treatment. I believe that the findings in this study provide an important insight that is critical to informing future global clinical trials on NSCLC using combinations of carboplatin and paclitaxel as first-line treatment and docetaxel as second-line treatment and foster the interpretation of efficacy results not only for the pharmaceutical industry but also for clinical researchers.

2. Materials and methods

2.1. Carboplatin and paclitaxel as first-line therapy

2.1.1. Trial selection and database construction

Articles of randomized clinical trials with chemotherapy regimens of carboplatin and paclitaxel as first-line therapy in patients with advanced NSCLC published between January 1, 2000 and December 31, 2013 were identified through a systematic search in PubMed. The following keywords were used, and results were limited to articles published in English: "non-small-cell lung," "carboplatin," "paclitaxel," "Phase II," "Phase III" and "randomized controlled trial". Trials included were randomized phase II or III clinical trials in advanced NSCLC patients treated with carboplatin and paclitaxel as first-line chemotherapy with the information on both OS and ORR. Trials were excluded for the following reasons by manual review: post-operative or pre-operative chemotherapy, other than first line therapy, chemoradiation therapy, other than paclitaxel plus carboplatin therapy, patient selection by biomarker, review/duplicate publication/sub analysis/ combined analysis, trials without information on efficacy data (both OS and ORR) or sufficient baseline patient characteristics, trials with the number of patients less than 40 and other than randomized trials. To avoid bias, two observers independently extracted data from the articles.

2.1.2. Data extraction

Extracted data included publication year, patient characteristics (age, gender, Performance Status (PS)), disease stage, histological type of NSCLC, treatment information (paclitaxel administration schedule), trial characteristics (phase, year of trial initiation, region (Asian or non-Asian trials), and number of patients), and efficacy information (median OS, PFS or TTP, and ORR). Asian trials were defined as those conducted in Japan, China or Taiwan. One Asian multinational trial which was conducted in Hong Kong, China, Indonesia, Japan, Malaysia, the Philippines, Singapore, Taiwan, and Thailand was included in this category since the majority

of patients were Japanese and Chinese. Non-Asian trials were defined as those conducted in US or European countries and some others. Multinational trials conducted in both Asian and non-Asian regions were classified as "others." Percentages of males, PS 2 or Karnofsky performance status of 50-60, stage IV disease, and adenocarcinoma were used as variables for gender, PS, disease stage, and histological type of NSCLC, respectively. OS and ORR were extracted for all the treatment arms using published data. Data on smoking status, weight loss and EGFR mutation were not included due to limited data availability in each of the articles.

2.1.3. Data analysis

The following analyses were performed on many heterogeneous studies with different kinds of patient characteristics to investigate potential factors that influence efficacy variables of median OS TTP/PFS and ORR.

Simple linear regression analyses were performed to investigate factors that influence efficacy variables of median OS and TTP/PFS using the following variables: number of patients, trial phase, year of trial initiation, region, paclitaxel administration schedule, median age, percentage of male patients, percentage of PS2 patients, percentage of patients with stage IV disease and percentage of patients with adenocarcinoma, taking the number of patients in each study into consideration. A $p<0.1$ was considered to identify potential factors for multiple linear regression analyses. Subsequently, using identified factors, multiple linear regression analyses with variable selection method (stepwise approach using $p < 0.05$) were performed to identify factors affecting OS and TTP/PFS.

In a similar manner, univariate logistic regression analyses were conducted for ORR using the same variables. A $p<0.1$ was considered to identify potential factors for multivariate logistic regression analyses. Subsequently, using identified factors, multivariate logistic regression analyses with variable selection method (stepwise approach using $p < 0.05$) were performed to

identify factors affecting ORR.

Mann-Whitney U test was used for comparisons of median OS, PFS/TTP and ORR between trials in Asian and non-Asian regions.

A $p < 0.05$ was considered statistically significant throughout the analyses except where otherwise noted. Analyses were performed using SAS (version 9.2; SAS Institute Inc., Cary, NC, USA) and StatsDirect (version 2.7.9; StatsDirect Ltd, Altrincham, Cheshire, UK).

2.2. Docetaxel as second-line therapy

2.2.1. Trial selection and database construction

Articles of randomized clinical trials with chemotherapy regimen of docetaxel as second-line therapy in patients with advanced NSCLC published between January 1, 2000 and December 31, 2014 were identified through a systematic search in PubMed. The following keywords were used, and results were limited to articles published in English: "non-small-cell lung," "docetaxel," "second line," "Phase II," "Phase III" and "randomized controlled trial". Trials included were randomized phase II or III clinical trials in advanced NSCLC patients treated with docetaxel as second line chemotherapy with the information on both OS and ORR. Trials in second or more line treatment of docetaxel were included. Trials were excluded for the following reasons by manual review: Other than second line therapy, other than docetaxel therapy, review/sub analysis, trials without information on efficacy data (both OS and ORR) or sufficient baseline patient characteristics, trials with the number of patients less than 25 and other than randomized trials. To avoid bias, two observers independently extracted data from the articles.

2.2.2. Data extraction

Extracted data included publication year, patient characteristics (age, gender, PS), disease stage, histological type of NSCLC, treatment information (docetaxel administration schedule and treatment line), trial characteristics (phase, year of trial initiation, region (Asian or non-Asian trials), and number of patients), and efficacy information (median OS, PFS or TTP, and ORR). Asian trials were defined as those conducted in Japan, China, Korea or Taiwan. Non-Asian trials were defined as those conducted in US or European countries and some others. Multinational trials conducted in both Asian and non-Asian regions were classified as “others.” Percentages of males, PS 2 or Karnofsky performance status of 50-60, stage IV disease, and adenocarcinoma were used as variables for gender, PS, disease stage, and histological type of

NSCLC, respectively. OS and ORR were extracted for all the treatment arms using published data. Data on smoking status, weight loss, first line or prior treatment and EGFR mutation were not included due to limited data availability in each of the articles.

2.2.3. Data analysis

The following analyses were performed on many heterogeneous studies with different kinds of patient characteristics to investigate potential factors that influence efficacy variables of median OS TTP/PFS and ORR.

Simple linear regression analyses were performed to investigate factors that influence efficacy variables of median OS and TTP/PFS using the following variables: number of patients, trial phase, year of trial initiation, region, docetaxel administration schedule, treatment line of decetaxel, median age, percentage of male patients, percentage of PS2 patients, percentage of patients with stage IV disease and percentage of patients with adenocarcinoma, taking the number of patients in each study into consideration. A $p<0.1$ was considered to identify potential factors for multiple linear regression analyses. Subsequently, using identified factors, multiple linear regression analyses with variable selection method (stepwise approach using $p < 0.05$) were performed to identify factors affecting OS and TTP/PFS.

In a similar manner, univariate logistic regression analyses were conducted for ORR using the same variables. A $p<0.1$ was considered to identify potential factors for multivariate logistic regression analyses. Subsequently, using identified factors, multivariate logistic regression analyses with variable selection method (stepwise approach using $p < 0.05$) were performed to identify factors affecting ORR.

Mann-Whitney U test was used for comparisons of median OS, PFS/TTP and ORR between trials in Asian or non-Asian regions and in patients with PS 2 of ≥15 or <15 %.

A $p < 0.05$ was considered statistically significant throughout the analyses except where

otherwise noted. Analyses were performed using SAS (version 9.2; SAS Institute Inc., Cary, NC, USA) and StatsDirect (version 2.7.9; StatsDirect Ltd, Altrincham, Cheshire, UK).

3. Results

3.1. Carboplatin and paclitaxel as first-line therapy

3.1.1. Trial Characteristics

The flowchart for trial selection is shown (Figure 1). A total of 333 articles were retrieved. As a result of manual literature review, 53 trials were ultimately selected to establish the database for the meta-analysis [9-61].

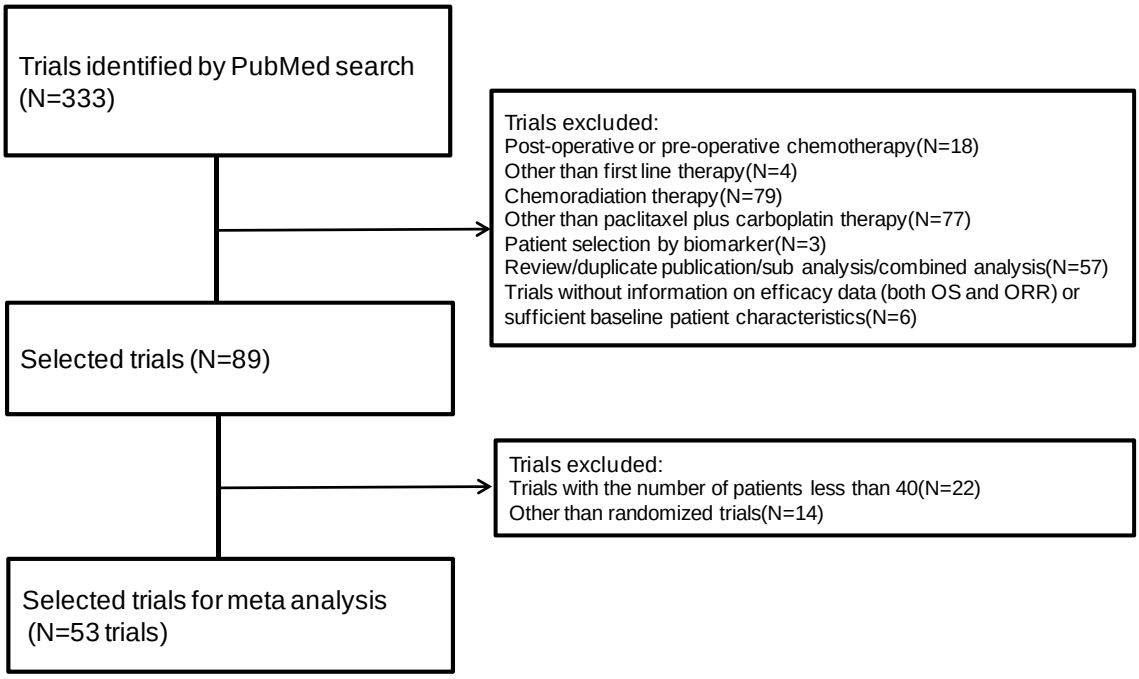

Figure 1 Flowchart of selecting trials for the analysis

ORR: overall response rate, OS : overall survival

Main characteristics of the 53 trials are listed (Table 1). A total of 61 treatment arms and 12,738 patients with advanced NSCLC were included. The median number of patients per trial was 159 (range 40–650) with most trials having a high proportion of males (67.0 %: range 20.9-100%). The median age was 63 years (range 54.0-77.4). There were 25 arms from phase II and 36 arms from phase III trials. Trials were classified into two groups by year of trial start, considering the timing of first approval of an EGFR TKI molecular-targeted agent: between 1995 and 2002 (36 arms) and between 2003 and 2008 (21 arms). The median OS was 9.5 months (range 5.9-23.4)

for all arms, and median PFS/TTP was 5.1 months (range 2.9–7.2) for 54 arms. The median overall response rate was 27.1% for all arms (range 12.0-60.9).

Table 1 Characteristics of 61 treatment arms in the selected trials for the analysis

Variables	Overall
Total number of trials	53
Total number of arms	61
Total number of patients	12,738
Number of randomized patients per arm	
<160	31
≥160	30
Median (range)	159 (40-650)
Phase [a]	
II	25 (41.0%)
III	36 (59.0%)
Year of trial initiation [a]	
1995-2002	36 (59.0%)
2003-2008	21 (34.4%)
unknown	4 (6.6%)
Trial Region [a]	
Asia	11 (18.0%)
Non-Asia	45 (73.8%)
Others	5 (8.2%)
Administration schedule of Paclitaxel [a]	
Weekly	9 (14.8%)
Every 3 weeks	52 (85.2%)
Median Age(range)	63 (54.0-77.4)
Percentage of male patients (range)	67 (20.9-100)
Percentage of PS2 patients (range)	3.3 (0-100)
Percentage of patients with Stage IV disease(range)	79.5 (39.7-98.0)
Percentage of patients with Adenocarcinoma (range)	52 (26.2-97.2)
ORR (%)(range)	27.1 (12.0-60.9)
PFS/TTP (months) (range)	5.1 (2.9-7.2)
OS (months) (range)	9.5 (5.9-23.4)

ORR: overall response rate, PFS: progression free survival, TTP: time to progression, OS: overall survival, PS: performance status

[a] Percentage per arm

3.1.2. Regression analysis

I selected year of trial initiation (1995–2002, 2003–2008), trial phase (II, III), trial region (Asia, non -Asia), number of patients (<160, ≥160), paclitaxel administration schedule (weekly, every 3 weeks), median age (<63, ≥63), percentage of male patients (<70, ≥70), percentage of PS2 patients (<10, ≥10), percentage of patients with stage IV disease (<80, ≥80), and percentage of patients with adenocarcinoma (<55, ≥55) as potential influencing factors.

Identification of factors influencing OS

In simple and linear regression analyses to identify factors influencing OS, year of trial initiation, trial region, median age and percentage of patients with adenocarcinoma were identified as factors potentially contributing to OS prolongation. Upon further multiple linear regression analyses, trial region (Asia) was identified as favorable factors significantly contributing to longer OS (Table 2).

Identification of factors influencing PFS/TTP

Year of trial initiation, percentage of male patients, percentage of patients with stage IV disease and percentage of patients with adenocarcinoma were identified as factors potentially contributing to PFS or TTP prolongation in simple and linear regression analyses. Further multiple linear regression analyses did not yield significant factors (Table 3).

Identification of factors influencing ORR

In univariate logistic regression analyses, trial region, paclitaxel administration schedule , percentage of male patients, percentage of PS2 patients, percentage of patients with stage IV disease and percentage of patients with adenocarcinoma were identified as factors potentially influencing ORR. Upon further multivariate logistic regression analyses, trial region (Asia), weekly administration schedule of paclitaxel, and patients with adenocarcinoma less than 55% of enrolled patients were identified as favorable factors significantly influencing ORR (Table 4).

Table 2 Factors influencing OS identified by linear regression analysis(Carboplatin and paclitaxel as first line therapy)

Characteristics	Category	N	Simple linear regression			Multiple linear regression		
			Regression coefficient	SE	P value	Regression coefficient	SE	P value
Year of trial initiation	2003-2008 1995-2002	21 36	2.611	0.587	<0.0001	Excluded	-	-
Phase	III II	36 25	0.221	0.912	0.8095	-	-	-
Trial Region	Non –Asia Asia	45 11	-5.922	0.589	< 0.0001	-5.895	0.684	< 0.0001
No. of randomized patients	≥160 <160	30 31	0.538	0.787	0.4969	-	-	-
Administration schedule of Paclitaxel	Every 3 weeks Weekly	52 9	1.169	0.979	0.2372	-	-	-
Median Age	≥63 <63	27 26	-1.237	0.694	0.0808	Excluded	-	-
% of male patients	≥70 <70	26 35	-0.840	0.650	0.2012	-	-	-
% of PS2 patients	≥10 <10	23 36	0.241	0.704	0.7334	-	-	-
% of patients with Stage IV disease	≥80 <80	30 30	-0.662	0.638	0.3037	-	-	-
% of patients with Adenocarcinoma	≥55 <55	25 26	1.733	0.658	0.0113	Excluded	-	-

OS : overall survival, PS: performance status, SE: standard error, N: number of treatment arms,

- : not used in the multiple regression analysis because $p > 0.1$, Excluded: excluded as a result of the step wise approach using $p < 0.05$

Table 3 Factors influencing PFS/TTP identified by linear regression analysis(Carboplatin and paclitaxel as first line therapy)

Characteristics	Category	N	Simple linear regression			Multiple linear regression		
			Regression coefficient	SE	P value	Regression coefficient	SE	P value
Year of trial initiation	2003-2008 1995-2002	21 31	0.584	0.227	0.0132	Excluded	-	-
Phase	III II	33 21	-0.162	0.389	0.6797	-	-	-
Trial Region	Non –Asia Asia	38 11	-0.414	0.398	0.3034	-	-	-
No. of randomized patients	≥160 <160	29 25	-0.052	0.343	0.8800	-	-	-
Administration schedule of Paclitaxel	Every 3 weeks Weekly	47 7	-0.621	0.400	0.1270	-	-	-
Median Age	≥63 <63	25 22	-0.201	0.250	0.4257	-	-	-
% of male patients	≥70 <70	25 29	0.441	0.259	0.0944	Excluded	-	-
% of PS2 patients	≥10 <10	21 32	0.004	0.287	0.9877	-	-	-
% of patients with Stage IV disease	≥80 <80	25 28	-0.498	0.253	0.0545	Excluded	-	-
% of patients with Adenocarcinoma	≥55 <55	23 24	-0.442	0.255	0.0890	Excluded	-	-

PFS: progression free survival, TTP: time to progression, PS: Performance Status, SE: standard error, N: number of treatment arms,

- : not used in the multiple regression analysis because $p > 0.1$, Excluded: excluded as a result of the step wise approach using $p < 0.05$

Table 4 Factors influencing ORR identified by logistic regression analysis (Carboplatin and paclitaxel as first line therapy)

Characteristics	Category	N	Univariate analysis			Multivariate analysis		
			OR	95%CI	P value	OR	95%CI	P value
Year of trial initiation	2003-2008 1995-2002	21 36	0.984	0.905-1.070	0.7031	-	-	-
Phase	III II	36 25	0.949	0.849-1.060	0.3547	-	-	-
Trial Region	Non -Asia Asia	45 11	0.743	0.661-0.833	< 0.0001	0.580	0.508-0.662	< 0.0001
No. of randomized patients	≥160 <160	30 31	0.988	0.897-1.088	0.8046	-	-	-
Administration schedule of Paclitaxel	Every 3 weeks Weekly	52 9	0.752	0.669-0.845	< 0.0001	0.815	0.716－0.929	0.0021
Median Age	≥63 <63	27 26	0.969	0.891-1.054	0.4631	-	-	-
% of male patients	≥70 <70	26 35	1.284	1.186-1.391	< 0.0001	Excluded	-	-
% of PS 2 patients	≥10 <10	23 36	1.170	1.075-1.273	0.0003	Excluded	-	-
% of patients with Stage IV disease	≥80 <80	30 30	0.832	0.769-0.900	< 0.0001	Excluded	-	-
% of patients with Adenocarcinoma	≥55 <55	25 26	0.792	0.729-0.861	< 0.0001	0.661	0.595－ 0.735	< 0.0001

ORR: overall response rate, OR: odds ratio, PS: performance status, CI: confidential interval, N: number of treatment arms,

- : not used in the multiple regression analysis because $p > 0.1$, Excluded: excluded as a result of the step wise approach using $p < 0.05$

3.2. Docetaxel as second-line therapy

3.2.1. Trial Characteristics

The flowchart for trial selection is shown (Figure 2). A total of 116 articles were retrieved. As a result of manual literature review, 31 trials were ultimately selected to establish the database for the meta-analysis [62-92].

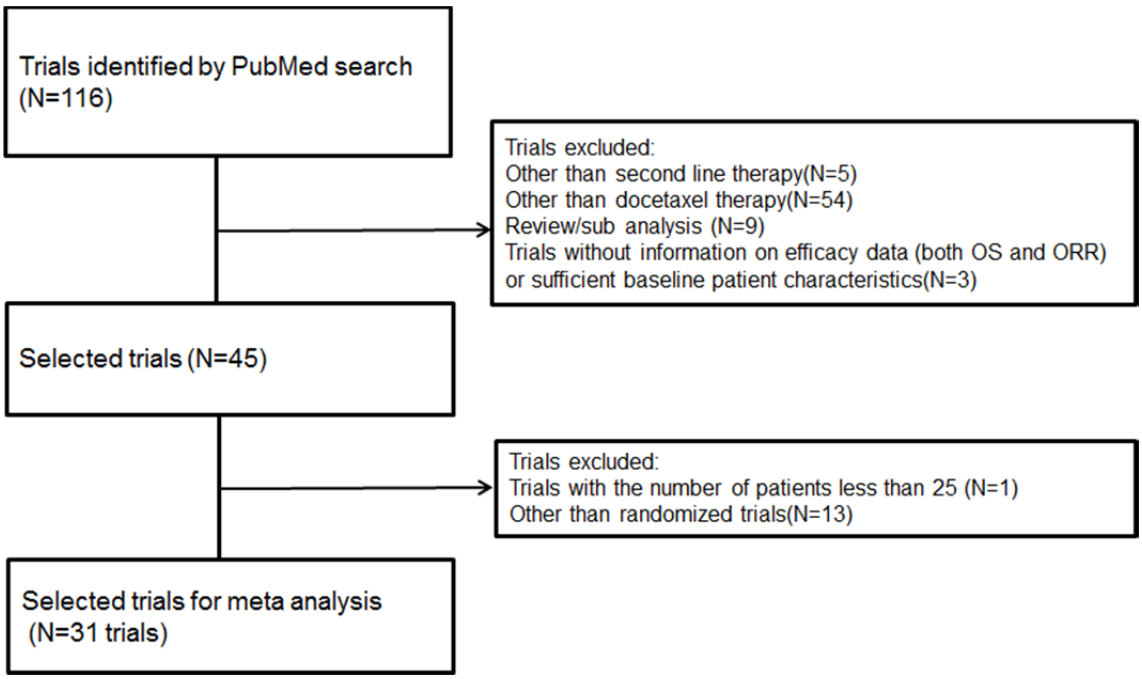

Figure 2 Flowchart of selecting trials for the analysis

ORR: overall response rate, OS : overall survival

Main characteristics of the 31 trials are listed (Table 5). A total of 39 treatment arms and 5,312 patients with advanced NSCLC were included. The median number of patients per trial was 73(range 25–697) with most trials having a high proportion of males (75.0 %: range 57.0-93.0%). The median age was 60 years (range 55.0-68.0). There were 19 arms from phase II and 20 arms from phase III trials. Classifications of trials by year of trial start were between 1998 and 2002 (20 arms) and between 2003 and 2010 (16 arms). The median OS was 7.4 months (range 4.7-22.9) for all arms, and median PFS/TTP was 2.8 months (range 1.4-4.8) for 37 arms. The median overall response rate was 8.8 % for all arms (range 2.1-24.0).

Table 5 Characteristics of 39 treatment arms in the selected trials for the analysis

Variables	Overall
Total number of trials	31
Total number of arms	39
Total number of patients	5,312
Number of randomized patients per arm	
<75	20
≥75	19
Median (range)	73 (25-697)
Phase [a]	
II	19 (48.7%)
III	20 (51.3%)
Year of trial initiation [a]	
1998-2002	20 (51.3%)
2003-2010	16 (41.0%)
Unknown	3 (7.7%)
Trial Region [a]	
Asia	10 (25.6%)
Non-Asia	24 (61.5%)
Others	5 (12.9%)
Treatment line of Docetaxel [a]	
Second line	30 (76.9%)
≥Second/ line	9 (23.1%)
Administration schedule of Docetaxel [a]	
Weekly	9 (23.1%)
Every 3 weeks	27 (69.2%)
Others	3(7.7%)
Median Age(range)	60.0 (55.0-68.0)
Percentage of male patients (range)	75.0 (57.0-93.0)
Percentage of PS2 patients (range)	15.0 (0-74.0)
Percentage of patients with Stage IV disease(range)	80.8 (48.0-100)
Percentage of patients with Adenocarcinoma (range)	48.3 (26.0-75.0)
ORR (%)(range)	8.8 (2.1-24.0)
PFS/TTP (months) (range)	2.8 (1.4-4.8)
OS (months) (range)	7.4 (4.7-22.9)

ORR: overall response rate, PFS: progression free survival, TTP: time to progression, OS: overall survival, PS: performance status

[a] number of treatment arms (%)

3.2.2. Regression analysis

I selected year of trial initiation (1998–2002, 2003–2010), trial phase (II, III), trial region (Asia, non -Asia), number of patients (<75, ≥75), docetaxel administration schedule (weekly, every 3 weeks), treatment line of docetaxel (second line, second or more line), median age (<60, ≥60), percentage of male patients (<75, ≥75), percentage of PS2 patients (<15, ≥15), percentage of patients with stage IV disease (<80, ≥80), and percentage of patients with adenocarcinoma (<50, ≥50) as potential influencing factors.

Identification of factors influencing OS

In simple and linear regression analyses to identify factors influencing OS, year of trial initiation, trial region, percentage of male patients, percentage of PS2 patients and percentage of patients with adenocarcinoma were identified as factors potentially contributing to OS prolongation. Upon further multiple linear regression analyses, trial region (Asia) and patients with PS 2 less than 15 % of enrolled patients were identified as favorable factors significantly contributing to longer OS (Table 6).

Identification of factors influencing PFS/TTP

Year of trial initiation, trial region, median age, percentage of male patients, percentage of PS 2 patients, percentage of patients with stage IV disease and percentage of patients with adenocarcinoma were identified as factors potentially contributing to PFS or TTP prolongation in simple and linear regression analyses. Upon further multiple linear regression analyses, patients with PS 2 less than 15 % of enrolled patients was identified as favorable factors significantly contributing to longer PFS/TTP (Table 7).

Identification of factors influencing ORR

In univariate logistic regression analyses, trial region, treatment line of docetaxel, percentage of male patients and percentage of patients with stage IV disease were identified as factors potentially influencing ORR. Upon further multivariate logistic regression analyses, second or

more line treatment of docetaxel, male patients less than 75% and patients with stage IV less than 80% of enrolled patients were identified as favorable factors significantly influencing ORR (Table 8).

Table 6 Factors influencing OS identified by linear regression analysis (Docetaxel as second line therapy)

Characteristics	Category	N	Simple linear regression			Multiple linear regression		
			Regression coefficient	SE	P value	Regression coefficient	SE	P value
Year of trial initiation	2003-2010 1998-2002	16 20	2.461	0.592	0.0002	Excluded	-	-
Phase	III II	20 19	1.172	0.861	0.1818	-	-	-
Trial Region	Non –Asia Asia	24 10	-4.176	0.828	<0.0001	-3.598	0.902	0.0003
No. of randomized patients	≥75 <75	19 20	0.417	0.882	0.6391	-	-	-
Treatment line of Docetaxel	≥Second/ line Second line	9 30	-0.428	0.945	0.6535	-	-	-
Administration schedule of Docetaxel	Every 3 weeks Weekly	27 9	1.687	1.050	0.1172	-	-	-
Median Age	≥60 <60	20 15	-0.329	0.756	0.6659	-	-	-
% of male patients	≥75 <75	20 19	-2.062	0.632	0.0024	Excluded	-	-
% of PS2 patients	≥15 <15	19 18	-2.795	0.596	<0.0001	-2.725	0.850	0.0041
% of patients with Stage IV disease	≥80 <80	15 14	0.498	0.821	0.5495	-	-	-
% of patients with Adenocarcinoma	≥50 <50	14 18	2.554	0.695	0.0009	Excluded	-	-

OS : overall survival, PS: performance status, SE: standard error, N: number of treatment arms,

- : not used in the multiple regression analysis because $p > 0.1$, Excluded: excluded as a result of the step wise approach using $p < 0.05$

Table 7 Factors influencing PFS/TTP identified by linear regression analysis (Docetaxel as second line therapy)

Characteristics	Category	N	Simple linear regression			Multiple linear regression		
			Regression coefficient	SE	P value	Regression coefficient	SE	P value
Year of trial initiation	2003-2010 1998-2002	16 18	0.409	0.238	0.0955	Excluded	-	-
Phase	III II	18 19	0.311	0.299	0.3054	-	-	-
Trial Region	Non –Asia Asia	22 10	-0.493	0.281	0.0892	Excluded	-	-
No. of randomized patients	≥75 <75	17 20	0.145	0.303	0.6354	-	-	-
Treatment line of Docetaxel	≥Second/ line Second line	9 28	0.200	0.324	0.5400	-	-	-
Administration schedule of Docetaxel	Every 3 weeks Weekly	26 8	-0.034	0.403	0.9328	-	-	-
Median Age	≥60 <60	18 15	-0.547	0.239	0.0292	Excluded	-	-
% of male patients	≥75 <75	18 19	-0.543	0.239	0.0297	Excluded	-	-
% of PS2 patients	≥15 <15	17 18	-0.640	0.244	0.0131	-1.163	0.375	0.0113
% of patients with Stage IV disease	≥80 <80	13 14	0.706	0.242	0.0074	Excluded	-	-
% of patients with Adenocarcinoma	≥50 <50	13 17	0.686	0.279	0.0205	Excluded	-	-

PFS: progression free survival, TTP: time to progression, PS: Performance Status, SE: standard error, N: number of treatment arms,

- : not used in the multiple regression analysis because $p > 0.1$, Excluded: excluded as a result of the step wise approach using $p < 0.05$

Table 8 Factors influencing ORR identified by logistic regression analysis (Docetaxel as second line therapy)

Characteristics	Category	N	Univariate analysis			Multivariate analysis		
			OR	95%CI	P value	OR	95%CI	P value
Year of trial initiation	2003-2010 1998-2002	16 20	1.016	0.837-1.233	0.8760	-	-	-
Phase	III II	20 19	0.859	0.680-1.085	0.2022	-	-	-
Trial Region	Non -Asia Asia	24 10	0.753	0.568-0.999	0.0494	Excluded	-	-
No. of randomized patients	≥75 <75	19 20	0.885	0.700-1.119	0.3075	-	-	-
Treatment line of Docetaxel	≥Second/ line Second line	9 30	1.262	0.990-1.610	0.0604	1.467	1.027-2.096	0.0353
Administration schedule of Docetaxel	Every 3 weeks Weekly	27 9	1.142	0.847-1.539	0.3852	-	-	-
Median Age	≥60 <60	20 15	1.019	0.835-1.243	0.8562	-	-	-
% of male patients	≥75 <75	20 19	0.692	0.561-0.852	0.0005	0.435	0.305-0.620	<0.0001
% of PS2 patients	≥15 <15	19 18	0.932	0.759-1.143	0.4965	-	-	-
% of patients with Stage IV disease	≥80 <80	15 14	1.730	1.385-2.161	<0.0001	0.563	0.368-0.860	0.0079
% of patients with Adenocarcinoma	≥50 <50	14 18	1.015	0.803-1.284	0.8984	-	-	-

ORR overall response rate, OR Odds ratio, PS: performance status, CI: confidential interval, N: number of treatment arm,

- : not used in the multiple regression analysis because $p > 0.1$, Excluded: excluded as a result of the step wise approach using $p < 0.05$

3.3. The comparison of overall outcomes

3.3.1. Outcomes between Asian and non-Asian trials

Carboplatin and paclitaxel as first-line therapy

In comparisons between Asian and non-Asian trials, significant differences in median OS (14.1 and 9.0 months, P< 0.0001) and ORR (32.4% and 25.6%, P=0.004) were identified, while median PFS/TTP was found not to be significantly different (5.8 and 4.9 months, P=0.1339) (Table 9 and Figure 3,4 and 5).

Table 9 Outcomes in Asian and non-Asian trials

Median OS			Median PFS/TTP			Median ORR		
Asian trials	Non- Asian trials	P*	Asian trials	Non-Asian trials	P*	Asian trials	Non-Asian trials	P*
14.1 (11)	9.0 (45)	<0.0001	5.8 (11)	4.9 (38)	0.1339	32.4% (11)	25.6% (45)	0.004

OS: overall survival, TTP: time to progression, PFS: progression-free survival, ORR: overall response rate, ( ) number of treatment arms

P* Mann-Whitney U test

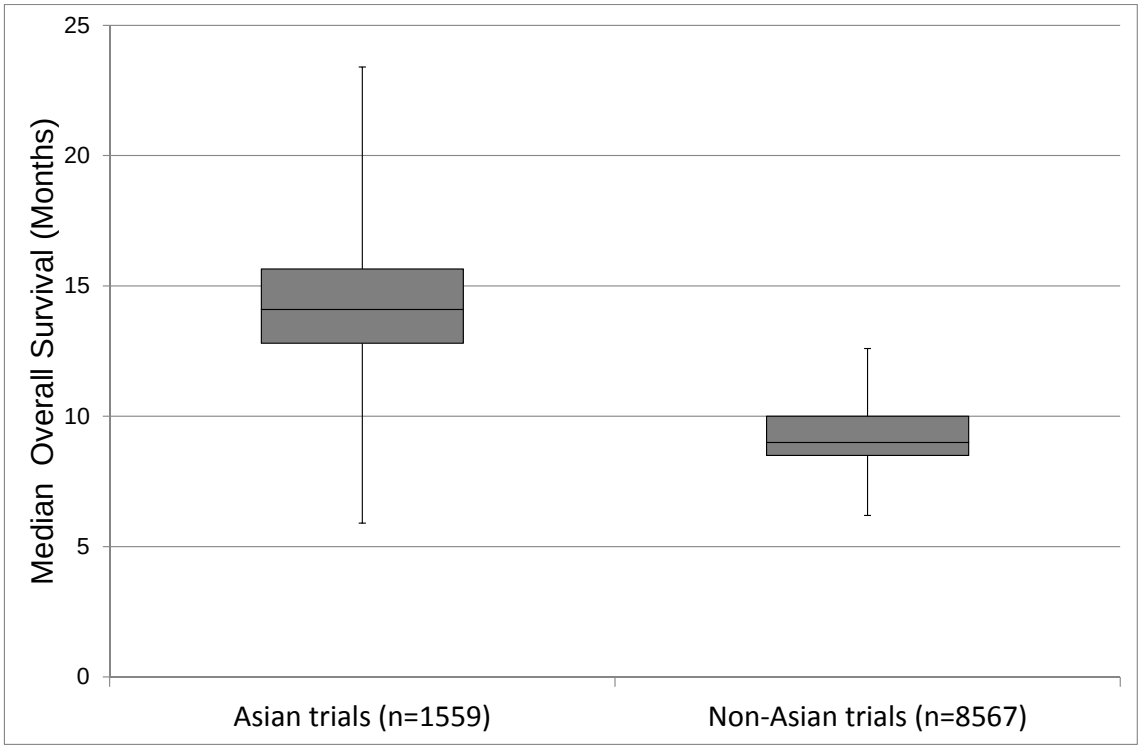

Figure 3 Median overall survival in Asian and non-Asian trials

( ) number of patients

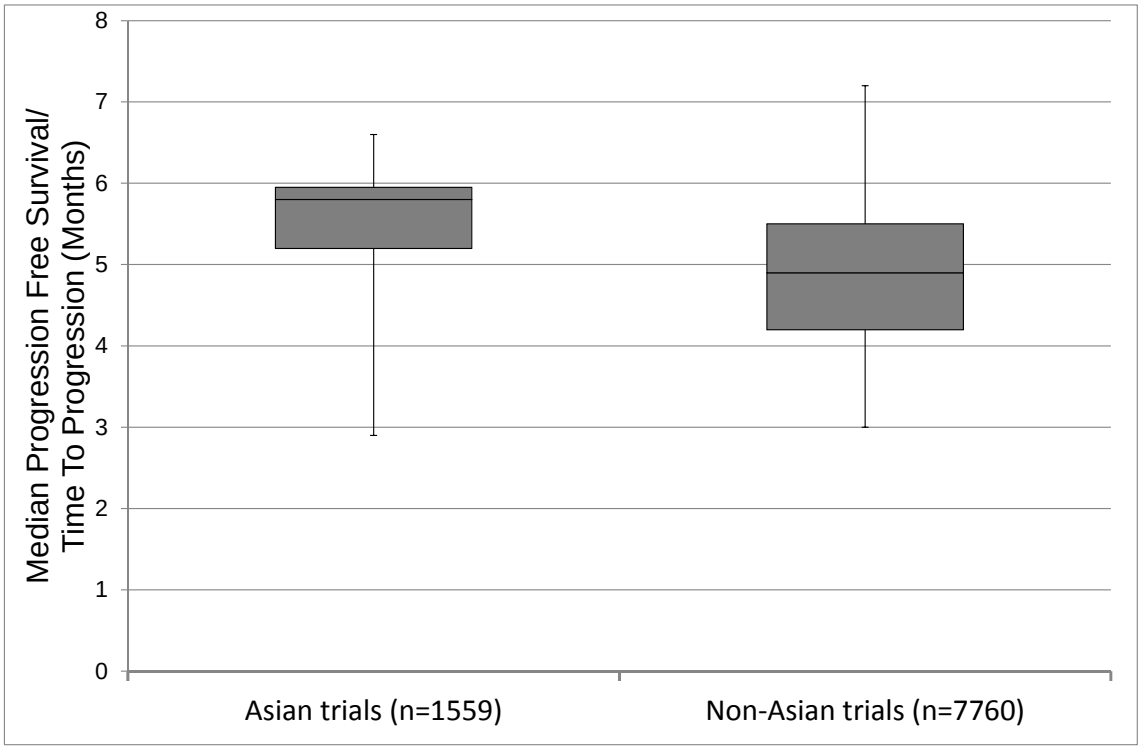

Figure 4 Median PFS/TTP in Asian and non-Asian trials

( ) number of patients

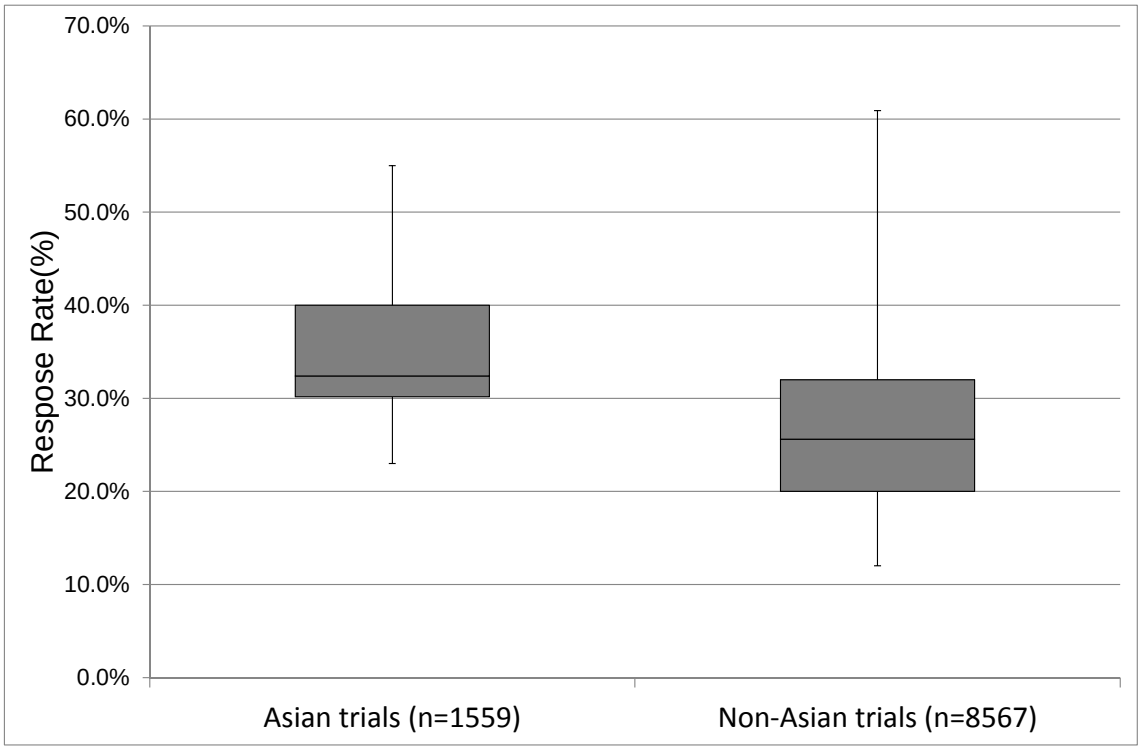

Figure 5 Overall response rate in Asian and non-Asian trials

( ) number of patients

Docetaxel as second-line therapy

In comparisons between Asian and non-Asian trials, significant differences in median OS (9.8 and 6.7 months, P＝0.0002) and PFS/TTP (3.2 and 2.7, P=0.0436) were identified, while median ORR was found not to be significantly different (11.5% and 8.3%, P=0.1733) (Table 10 and Figure 6, 7 and 8).

Table 10　Outcomes in Asian and non-Asian trials

Median OS			Median PFS/TTP			Median ORR		
Asian trials	Non- Asian trials	P*	Asian trials	Non-Asian trials	P*	Asian trials	Non-Asian trials	P*
9.8 (10)	6.7(24)	0.0002	3.2 (10)	2.7 (22)	0.0436	11.5% (10)	8.3% (24)	0.1733

OS: overall survival, TTP: time to progression, PFS: progression-free survival, ORR: overall response rate, ( ) number of treatment arms

P* Mann-Whitney U test

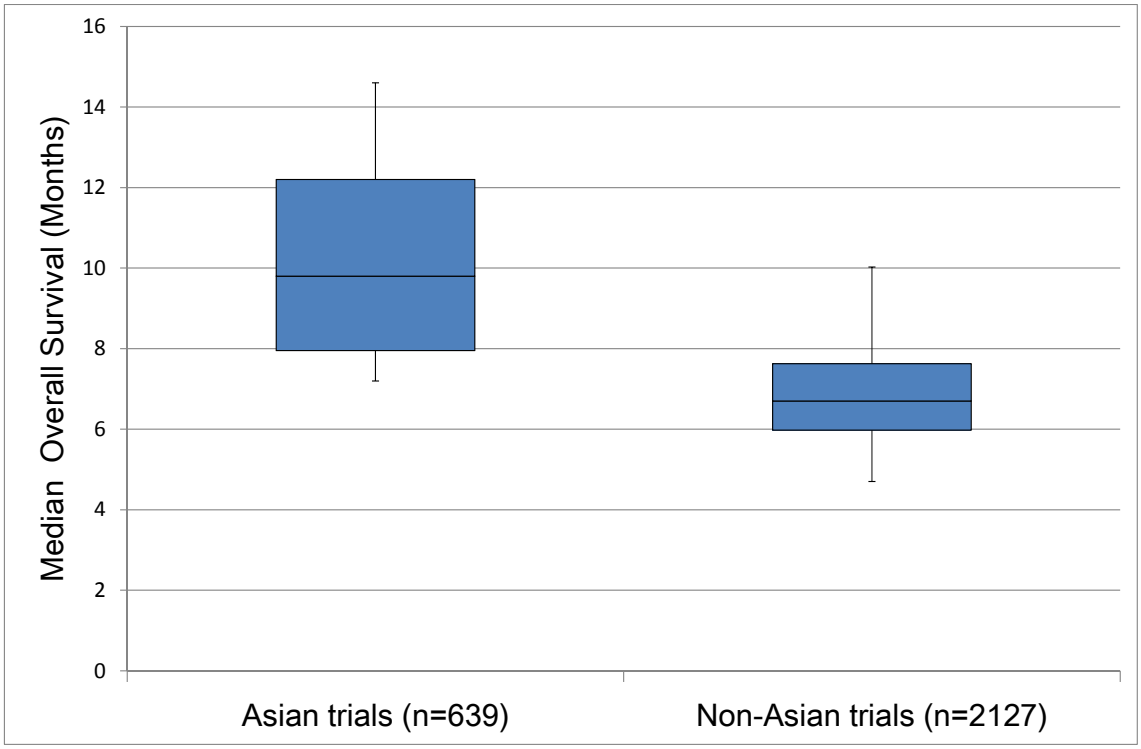

Figure 6　Median overall survival in Asian and non-Asian trials

( ) number of patients

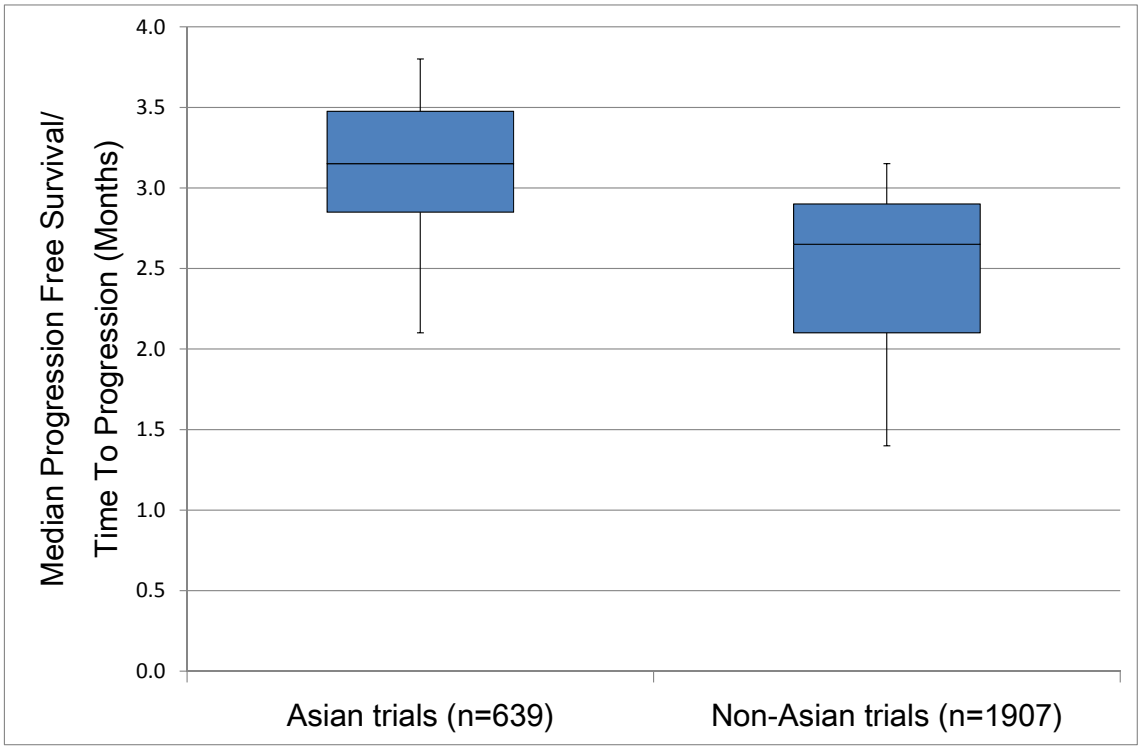

Figure 7 Median PFS/TTP in Asian and non-Asian trials

( ) number of patients

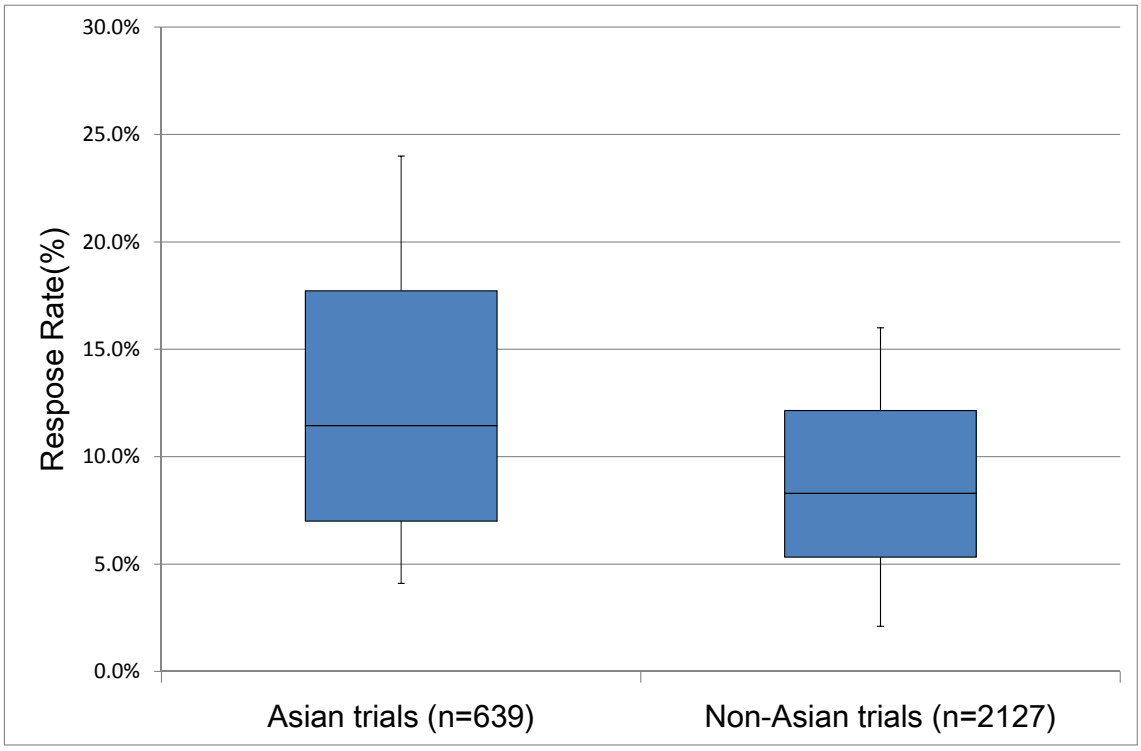

Figure 8 Overall response rate in Asian and non-Asian trials

( ) number of patients

3.3.2. Outcomes between trials treated with docetaxel as second line therapy in percentage of PS 2 patients

In comparisons between trials treated with docetaxel as second line therapy in patient with PS 2 of ≥15 and <15%, significant differences in median OS (9.2 and 6.7 months, P=0.0005) and PFS/TTP (3.1 and 2.6, P=0.031) were identified, while median ORR was found not to be significantly different (10.3% and 8.0%, P=0.3386) (Table 11 and Figure 9, 10 and 11).

Table 11 Outcomes in trials in patient with PS 2 of ≥15 and <15%

Median OS			Median PFS/TTP			Median ORR		
PS2 <15%	PS2≥15 %	P*	PS2 <15%	PS2≥15 %	P*	PS2 <15%	PS2≥15 %	P*
9.2(18)	6.7(19)	0.0005	3.1 (18)	2.6 (17)	0.031	10.3% (18)	8.0% (19)	0.3386

OS: overall survival, TTP: time to progression, PFS: progression-free survival, ORR: overall response rate, ( ) number of treatment arms

P* Mann-Whitney U test

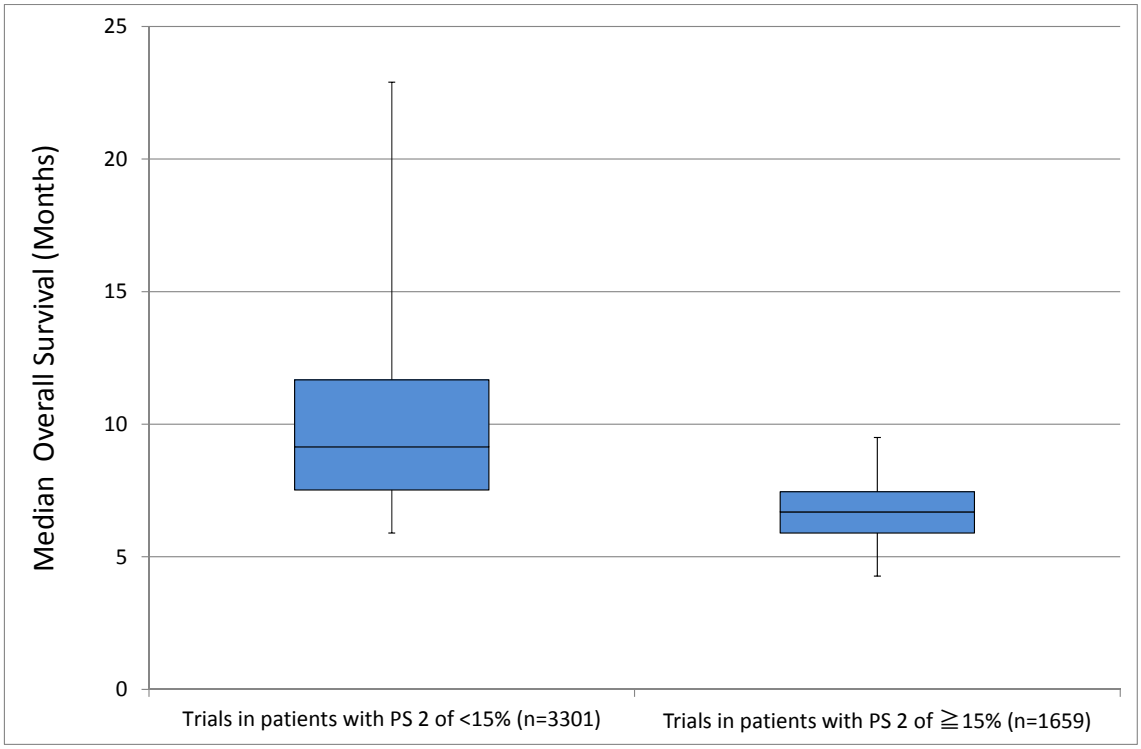

Figure 9 Median overall survival in trials in patient with PS 2 of ≥15 and <15%

( ) number of patients

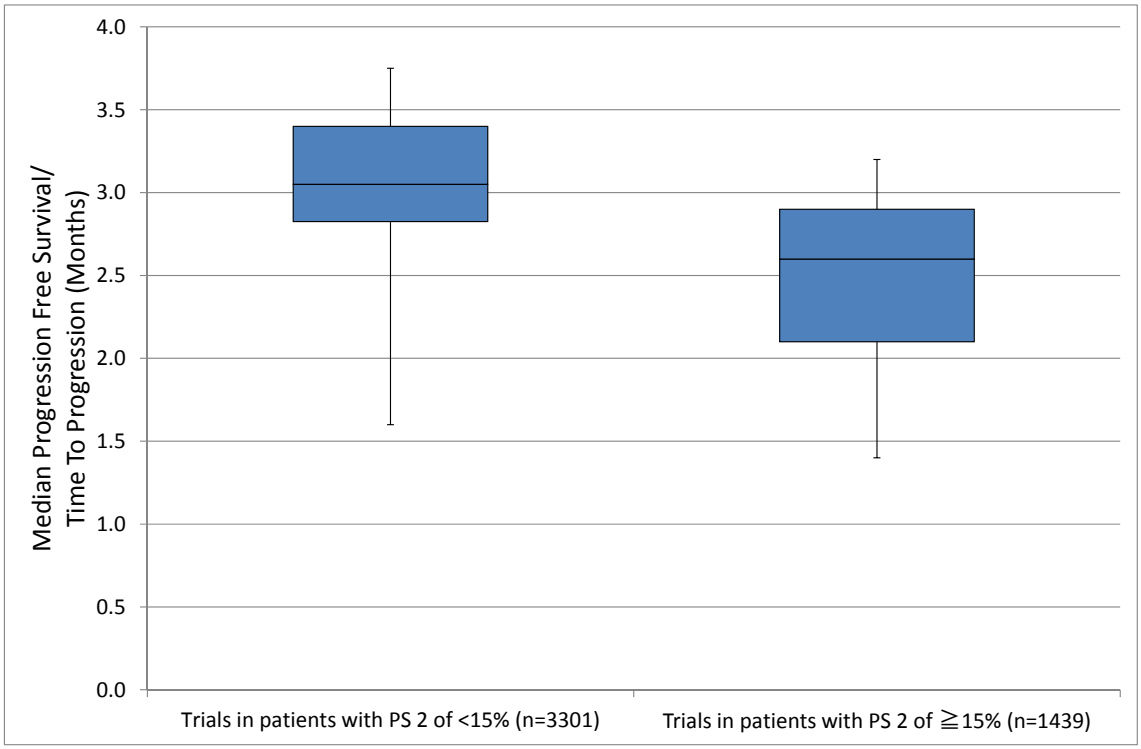

Figure 10　Median PFS/TTP in trials in patient with PS 2 of ≥15 and <15%

( ) number of patients

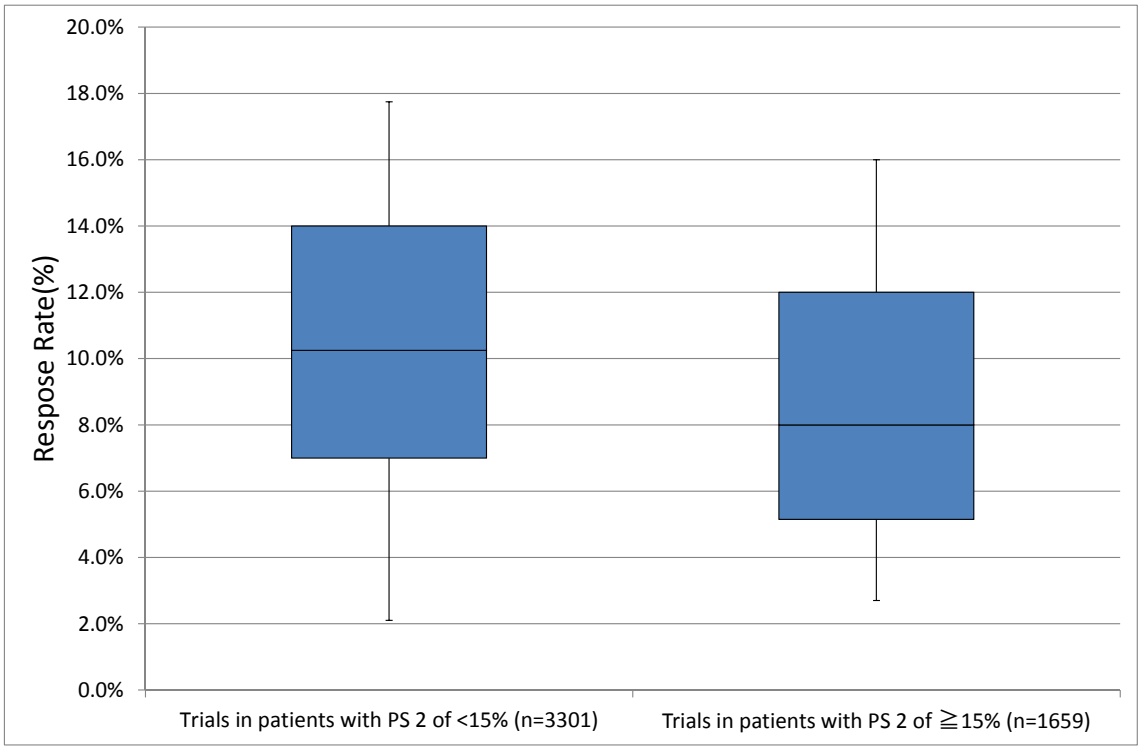

Figure 11　Overall response rate in trials in patient with PS 2 of ≥15 and <15%

( ) number of patients

4. Discussion

4.1. Comparison of prognostic factors influencing OS, PFS, and ORR in each of the carboplatin/paclitaxel and docetaxel treatment groups

4.1.1. Carboplatin and paclitaxel as first-line therapy

When the result for ORR was compared with that for PFS, trial region (Asia), administration schedule of paclitaxel (weekly), and percentage of patients with adenocarcinoma (<55% of enrolled patients) were identified as factors contributing to higher ORR. However, none of these factors were identified as factors potentially influencing PFS. This suggests that none of the factors influencing ORR may contribute to PFS prolongation. Furthermore, when the result for PFS was compared with that for OS, no factors influencing PFS were identified, whereas trial region (Asia) was identified as a factor contributing to OS prolongation. Higher ORR did not appear to have any direct relation to OS prolongation in Asian trials. OS prolongation may be attributed to the treatment administered following treatment with carboplatin and paclitaxel as first-line chemotherapy in Asian trials.

4.1.2. Docetaxel as second-line therapy

When the result for ORR was compared with that for PFS, treatment line of docetaxel (second- or more line treatment), proportion of male patients (<75% of enrolled patients), and proportion of patients with Stage IV disease (<80% of enrolled patients) were identified as factors contributing to higher ORR. The proportion of patients with PS 2 (<15% of enrolled patients) was identified as a factor contributing to PFS prolongation. This suggests that none of the factors influencing ORR may contribute to PFS prolongation. When the result for PFS was compared with that for OS, the proportion of patients with PS 2 (<15% of enrolled patients) was identified as a factor contributing to PFS prolongation, whereas trial region (Asia) and proportion of patients with PS 2 (<15% of enrolled patients) were identified as factors contributing to OS prolongation. Good performance status may contribute to PFS prolongation that may be related to OS prolongation. Furthermore, trial region (Asia) was not identified as a

factor influencing PFS. Thus, as observed for carboplatin and paclitaxel as first-line chemotherapy, OS prolongation may be attributed to the treatment administered following treatment with docetaxel as second-line chemotherapy in Asian trials.

4.2. Comparison of prognostic factors affecting OS, PFS, and ORR between carboplatin/paclitaxel and docetaxel treatment groups

When prognostic factors influencing OS, PFS, and ORR were compared between carboplatin/paclitaxel and docetaxel treatment groups, the trial region (Asia) was identified as a common factor contributing to OS prolongation. In general, either administration of TK inhibitors, chemotherapy (for patients ineligible for treatment with TK inhibitors), or supportive care is available for subsequent treatment following treatment with carboplatin/paclitaxel as first-line chemotherapy and docetaxel as second-line chemotherapy. It has been reported that EGFR mutation is a prognostic factor for a favorable outcome of patients with NSCLC treated with TKIs, such as gefitinib and elrotinib [93-98], and such mutations are more frequently observed in East-Asians compared with Americans and non-East Asians [99-102]. Treatment with TKIs as a subsequent therapy may play a role in the OS benefit observed in Asian regions. Also, one of the common factors in these treatment options, management of subsequent treatment, may differ between Asian and non-Asian regions. Subsequent treatment options may be selected according to either established treatment guidelines or daily medical practice within affordable range of patient financial burden for medical care. More specifically, differences in the health insurance system in each country may lead to differences in the management of subsequent treatment because a cost of molecular targeted drugs such as TKIs and genetic test before TKIs treatment is typically high all over the word. Health insurance systems differ depending on the country in terms of organization (public or private), coverage area, patient charge, and so on. These differences may correlate with the opportunity of accessing subsequent

treatments. Furthermore, it is assumed that the ability to access specialized hospitals during cancer treatment differs among each country [103-104]. Patients can receive well-supported treatment in line with the established treatment guideline at specialized hospitals because there is enough expertized medical staff and a leading-edge diagnostic test such as a screening of EGFR mutation is implemented. On the other hand, patients receive affordable treatment without choices at non-specialized hospitals according to daily medical practice. These differences may correlate with those of OS. Therefore, it is important to collect data on subsequent treatment in clinical trials to support these points.

In the docetaxel group, the proportion of patients with PS 2 (<15% of enrolled patients) was identified as a factor contributing to both PFS and OS prolongation, whereas in the carboplatin/paclitaxel treatment groups, the proportion of patients with PS 2 was not identified as a factor influencing PFS nor OS. On the basis of this result, PFS prolongation may be attributed to good PS during treatment with docetaxel as second-line chemotherapy, and PFS prolongation may continuously contribute to OS prolongation.

4.3. Points to consider for clinical trials assessing efficacy of novel agents combined with standard chemotherapy for NSCLC treatment

Our analysis demonstrated that in clinical trials on patients with NSCLC treated with carboplatin/paclitaxel and docetaxel, patients in Asian trials had a better OS than those in non-Asian trials. OS prolongation may be attributed to the subsequent treatment in Asian trials that suggests that the overall OS measurement of novel agents combined with carboplatin/paclitaxel and docetaxel can be skewed by the effect of subsequent therapies in Asian regions. However, it is clinically meaningful to measure OS as a primary endpoint in global clinical trials on patients with NSCLC because OS directly provides universal evidence of clinical benefit of the agent across regions.

OS is a gold standard endpoint for confirmatory phase III clinical trials assessing the efficacy of novel agents for the treatment of NSCLC because the true clinical benefit of therapeutic agents can be evaluated through this measure [105]. Using OS as a primary endpoint, more large-scale studies, including >1,000 patients, are expected to be conducted. Large-scale clinical trials have to rely on multinational trials, and it is difficult to repeatedly conduct similar trials. Therefore, it is very important to prepare proactive measures towards bringing the clinical trial to a successful result. In the present study, trial region (Asia) and low proportion of patients with PS 2 were identified as prognostic factors contributing to OS prolongation. When designing global phase III trials, this information is critical to assessing the efficacy of novel therapeutic agents in combination with carboplatin/paclitaxel or docetaxel. Adjustment without excessive bias of the ratio of the number of patients per region and addition of race and region as stratification factors should be considered. Furthermore, the ratio of the number of patients with PS 2 should be adjusted within the range of general medical practice in clinical trials of novel agents combined with docetaxel as second-line chemotherapy.

In diseases with a relatively long OS, such as NSCLC, OS may be strongly affected by the subsequent treatment; hence, OS prolongation may be attributed to the subsequent treatment after disease progression. Owing to this factor, treatment response to subsequent therapies is suggested to differ among countries. Thus, information regarding the subsequent treatment should be collected in clinical trials to completely understand its influence on OS.

4.4. Limitation

The present meta-analysis has a few limitations. First, we conducted the analysis on the basis of limited data that were available through publications of clinical trial results and not on individual patient data. In general, meta-analyses on the basis of individual patient data can be

used to more carefully investigate the influence of covariates on the heterogeneity of treatment effect both within and between trials and would provide robust estimates [106]. Second, data on the rate of EGFR mutation and subsequent treatment after disease progression were not included in our meta-analysis because of the limited data availability; such data may be important to develop a better understanding of prognostic factors influencing OS.

5. Conclusion

In conclusion, the region of Asia was identified as a prognostic factor of prolonged OS in treatment with carboplatin and paclitaxel as first-line chemotherapy and docetaxel as second-line chemotherapy. In addition, we identified a low proportion of patients with PS 2 as a factor contributing to longer OS in treatment with docetaxel as second-line chemotherapy. The findings of the present study reflect actual medical practice and circumstances with various patient backgrounds irrespective of the subsequent treatments in line with either established guidelines or daily medical practice in each county, which are expected to continue. More global clinical trials on NSCLC are expected to be conducted across regions and our finding, i.e., regional differences between Asian and non-Asian population, including Caucasians, should be considered in study design and interpretation of results of global clinical trials. Furthermore, the ratio of patients with PS 2 should be considered in the design of global clinical trials of novel agents used in combination with docetaxel as second-line chemotherapy.

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8. Supplementary data

Table 12 Detailed data of selected trials (Carboplatin and paclitaxel as first line therapy)

Trial	Reference	Year of trial initiation	phase	Trial region	Administration schedule of paclitaxel	No of pts (CP arm)	Age	Male pts	PS2 pts	Pts with Adeno	pts with stage IV	ORR	PFS/TTP	OS
Scagliotti GV et al, 2012	[9]	2007	III	Others	Every 3 weeks	549	60	61%	NA	81%	86%	26%	5.4	11
Lilenbaum R, et al, 2008	[10]	2002	II	Non-Asia	Every 3 weeks	51	NA	55.0%	100.0%	62.7%	86%	12%	3.5	9.5
Lynch TJ et al 2012	[11]	2008	II	Non-Asia	Every 3 weeks	66	62	74%	0.0%	58%	74%	14%	4.21	8.28
Niho S et al, 2012	[12]	2007	II	Asia	Every 3 weeks	59	60	64%	0.0%	93%	71%	31%	5.9	23.4
Soria JC et al,2011	[13]	2007	II	Non-Asia	Every 3 weeks	41	62	59%	0.0%	37%	98%	39%	6.1	10.1
Quoix E et al	[14]	2006	III	Non-Asia	Weekly	225	77.4	71.6%	27.1%	50.7%	80%	27.1%	6	10.3
Lara PN Jr et al 2011	[15]	2008	III	Others	Every 3 weeks	650	61	62.3%	0.0%	67.1%	90.9%	24.6%	5.5	12.7
Hirsh V et al	[16]	2005	III	Others	Every 3 weeks	420	62	65%	0.7%	58%	88%	23%	4.7	9.8
Digumarti R et al 2011	[17]	2004	II	Non-Asia	Every 3 weeks	55	56.1	84%	0.0%	NA	62%	27%	4.2	8.5
Han B et al 2011	[18]	2007	II	Asia	Every 3 weeks	61	58	62.3%	3.3%	67.2%	59%	23%	6.3	15.8
Saito H at al 2012	[19]	2001	II	Asia	Every 3 weeks	41	65	73.2%	100.0%	65.9%	82.9%	29.3%	2.9	5.9

Trial	Reference	Year of trial initiation	phase	Trial region	Administration schedule of paclitaxel	No of pts (CP arm)	Age	Male pts	PS2 pts	Pts with Adeno	pts with stage IV	ORR	PFS/TTP	OS
Biesma B et al 2011	[20]	2003	III	Non-Asia	Every 3 weeks	91	74	76%	15.0%	30%	69%	19%	4.5	6.9
Weissman CH et al 2011	[21]	2004	III	Non-Asia	Every 3 weeks	192	64	56.3%	0.0%	55.2%	84.4%	22.4%	4.67	9.24
Okamoto I et al 2010	[22]	2006	III	Asia	Every 3 weeks	281	63	76.5%	0.0%	69.4%	75.8%	29%	4.8	13.3
Belani CP et all 2008	[23]	2000	III	Non-Asia	Weekly	223	65	60%	12.0%	57%	82%	27.6%	4.23	8.88
Belani CP et all 2008	[23]	2000	III	Non-Asia	Every 3 weeks	221	65	65%	10.0%	58%	83%	19.2%	3.84	9.87
Goss GD 2010	[24]	2005	II	Non-Asia	Every 3 weeks	125	58	59%	0.0%	48%	NA	16%	5	10.1
Blumenschein GR et al 2008	[25]	2002	III	Non-Asia	Every 3 weeks	306	63	66%	0.0%	50%	87%	23.5%	4.9	9.2
Scagliotti G, et al 2010	[26]	2006	III	Others	Every 3 weeks	462	63.0	62%	0.0%	59%	90%	24.0%	5.4	10.6
Herbst RS et all 2005	[27]	2001	III	Non-Asia	Every 3 weeks	539	63	61.6%	0.2%	61.4%	82.2%	19.3%	4.9	10.5
Herbst RS et al 2004	[28]	2000	III	Non-Asia	Every 3 weeks	345	63	61.4%	9.3%	51.9%	78.3%	28.7%	5.0	9.9
Leighl NB et al 2005	[29]	2000	III	Non-Asia	Every 3 weeks	387	61.4	73%	11.0%	52%	79%	33.7%	5.3	9.2

Trial	Reference	Year of trial initiation	phase	Trial region	Administration schedule of paclitaxel	No of pts (CP arm)	Age	Male pts	PS2 pts	Pts with Adeno	pts with stage IV	ORR	PFS/TTP	OS
Lilenbaum RC et al 2005	[30]	1997	III	Non-Asia	Every 3 weeks	284	64	68%	17.0%	51%	87%	30%	NA	8.8
Heymach JV et al 2008	[31]	2004	II	Non-Asia	Every 3 weeks	52	59	71%	0.0%	50%	90%	25%	5.3	12.6
Langer C et al 2007	[32]	2000	II	Non-Asia	Every 3 weeks	51	65	74%	100.0%	51%	79%	14%	3.5	6.2
Paccagnella A et al 2006	[33]	1998	III	Non-Asia	Every 3 weeks	159	61	82%	6.0%	43%	64%	20%	5.1	8.3
Williamson SK et al 2005	[34]	2000	III	Non-Asia	Every 3 weeks	186	62.6	63%	0.0%	NA	87%	35%	5	9
Ohe Y et al 2007	[35]	2000	III	Asia	Every 3 weeks	145	63	68.3%	0.0%	72%	81%	32.4%	4.5	12.3
Kubota K, et al 2008	[36]	2001	III	Asia	Every 3 weeks	197	65	69%	0.0%	76%	83%	37.1%	5.8	14.1
Sakakibara T et al 2010	[37]	2004	II	Asia	Weekly	42	74	90%	0.0%	52%	60%	55%	6.0	14.7
Sakakibara T et al 2010	[37]	2004	II	Asia	Every 3 weeks	40	75	77.5%	0.0%	42.5%	55%	53%	5.6	15.5
Stathopoulos GP et al 2004	[38]	2000	III	Non-Asia	Every 3 weeks	185	65	86.5%	20.0%	44.3%	49.2%	46.0%	7	11
Scagliotti GV etal 2002,	[39]	1998	III	Non-Asia	Every 3 weeks	201	62	76%	8.0%	48%	82%	32%	5.5	10

Trial	Reference	Year of trial initiation	phase	Trial region	Administration schedule of paclitaxel	No of pts (CP arm)	Age	Male pts	PS2 pts	Pts with Adeno	pts with stage IV	ORR	PFS/TTP	OS
Schiller JH, et al2002	[40]	1996	III	Non-Asia	Every 3 weeks	299	63	62%	5.0%	NA	86%	17%	3.1	8.1
Rosell R, et al 2002	[41]	1996	III	Non-Asia	Every 3 weeks	309	58	83%	17.0%	47%	62%	25%	3	8.5
Sandler A et al 2006	[42]	2001	III	Non-Asia	Every 3 weeks	433	NA	58%	0.0%	88%	78%	15.1%	4.5	10.3
Belani CP et al 2005	[43]	1995	III	Non-Asia	Every 3 weeks	190	NA	66%	0.0%	NA	77%	23%	3.98	7.66
Kosmidis P, et al 2002	[44]	1998	III	Non-Asia	Every 3 weeks	238	63	87.0%	14.0%	47.0%	62.0%	28%	6.3	10.4
Kelly K et al 2001	[45]	1996	III	Non-Asia	Every 3 weeks	206	62	70%	0.0%	NA	88%	25%	4	8.6
Treat JA et al	[46]	2000	III	Non-Asia	Every 3 weeks	379	64.1	60.9%	0.3%	83.9%	89.4%	29.8%	4.7	8.7
Mok TS et al	[47]	2006	III	Asia	Every 3 weeks	608	57	20.9%	10.7%	97.2%	76.2%	32.2%	5.8	17.3
Langer CJ et al 2008	[48]	2002	III	Non-Asia	Every 3 weeks	201	63	78%	100.0%	NA	73%	37%	4.56	7.85
Pathak AK et al 2005	[49]	1998	II	Non-Asia	Every 3 weeks	72	54	83.6%	NA	26.2%	39.7%	33%	NA	9
Lilenbaum RC et al 2005	[50]	2000	II	Non-Asia	Every 3 weeks	83	63	51%	16.0%	NA	81%	16.9%	4.8	8.6
Chen YM et al 2006	[51]	2000	II	Asia	Every 3 weeks	40	NA	100%	47.5%	40%	82.5%	40%	6.6	10.3

Trial	Reference	Year of trial initiation	phase	Trial region	Administration schedule of paclitaxel	No of pts (CP arm)	Age	Male pts	PS2 pts	Pts with Adeno	pts with stage IV	ORR	PFS/TTP	OS
Chen YM et al 2002	[52]	1999	II	Asia	Every 3 weeks	45	NA	77.7%	35.6%	48.9%	62.2%	40%	5.7	14.1
Marsland TA et al2005	[53]	1999	II	Non-Asia	Weekly	60	NA	60%	28.3%	NA	70.5%	60.9%	NA	9.2
Belani CP ,et al 2003	[54]	1998	II	Non-Asia	Weekly	132	65	59%	14.0%	56%	77.0%	32%	6.9	11.3
Belani CP ,et al 2003	[54]	1998	II	Non-Asia	Weekly	130	63	65%	14.0%	47%	77.0%	24%	4.8	7.1
Belani CP ,et al 2003	[54]	1998	II	Non-Asia	Weekly	128	64	61%	15.0%	58%	78.0%	18%	6.2	9.2
Socinski MA, et al 2006	[55]	NA	II	Non-Asia	Every 3 weeks	81	61	67.0%	0.0%	NA	88%	32%	NA	6.6
Socinski MA, et al 2006	[55]	NA	II	Non-Asia	Weekly	80	60	62.0%	0.0%	NA	88%	36%	NA	8.7
Kosmidis P et al 2000	[56]	1996	II	Non-Asia	Every 3 weeks	99	62.4	89%	15.0%	38.4%	71%	25.6%	4.3	9.5
Kosmidis P et al 2000	[56]	1996	II	Non-Asia	Every 3 weeks	99	59.4	85%	10.0%	38.4%	69%	31.8%	6.4	11.4
Socinski MA,et al 2002	[57]	1998	III	Non-Asia	Every 3 weeks	114	62	63%	0.0%	78%	88%	22%	NA	6.6
Socinski MA,et al 2002	[57]	1998	III	Non-Asia	Every 3 weeks	116	66	62%	0.0%	78%	86%	24%	NA	8.5

Trial	Reference	Year of trial initiation	phase	Trial region	Administration schedule of paclitaxel	No of pts (CP arm)	Age	Male pts	PS2 pts	Pts with Adeno	pts with stage IV	ORR	PFS/TTP	OS
Schuette W et al 2006	[58]	NA	III	Non-Asia	Weekly	457	NA	81%	6.0%	39%	69%	38%	6.1	8.9
Schuette W et al 2006	[58]	NA	III	Non-Asia	Every 3 weeks	464	NA	83%	7.0%	41%	72%	33%	7.2	9.5
Laurie SA et al	[59]	2008	III	Non-Asia	Every 3 weeks	153	62	54%	0.0%	65%	95%	34%	5.5	12.1
Paz-Ares L et al 2013	[60]	2008	II	Non-Asia	Every 3 weeks	59	62	69%	0.0%	56%	90%	25%	5.5	7.8
Socinski MA et al 2012	[61]	2007	III	Others	Every 3 weeks	531	60	75%	0.03%	50%	79%	25%	5.8	11.2

Adeno: Adenocarcinoma, CP: Carboplatin and paclitaxel, NA: Not available, pts: patients, ORR: overall response rate, OS: overall survival, PFS: progression-free survival, PS: performance status

Table 13 Detailed data of selected trials (Docetaxel as second line therapy)

Trial	Reference	Year of trial initiation	phase	treatment line of docetaxel	Trial region	Administration schedule of docetaxel	No of pts (Doc arm)	Age	male pts	PS2 pts	Pts with Adeno	Pts with Stage IV	ORR	PFS/TTP	OS
Garon EB et al 2014	[62]	2010	III	2	Others	Every 3 weeks	625	61	66.0%	0.0%	NA	100%	14%	3.0	9.1
Kawaguchi T et al 2014	[63]	2009	III	2,3	Asia	Every 3 weeks	151	67	70.9%	4.0%	68.2%	80.8%	17.9%	3.2	12.2
Reck M et al 2014	[64]	2008	III	2	Others	Every 3 weeks	659	60	72.7%	0.0%	51.0%	61.9%	3.3%	2.7	9.1
Garassino MC et al 2013	[65]	2007	III	2	Non-Asia	Others	110	67	66.0%	6.0%	75.0%	NA	15.5%	2.9	8.2
Sun Y et al 2013	[66]	2006	III	2	Asia	Every 3 weeks	104	55.8	58.7%	10.6%	70.2%	80.8%	4.1%	3.1	12.2
Manegold C et al 2013	[67]	1999	II	2	Non-Asia	Every 3 weeks	34	NA	65.0%	21.0%	26.0%	91.0%	15.0%	2.2	6.4
Belvedere O et al 2011	[68]	2005	II	2	Non-Asia	Every 3 weeks	25	60	80.0%	0.0%	36.0%	92.0%	8.0%	1.7	7.1
Ready N et al 2011	[69]	2007	II	2	Non-Asia	Every 3 weeks	52	59.5	75.0%	14.0%	27%	48.0%	2.1%	1.6	5.9
Vergnenegre A et al 2011	[70]	2006	III	2	Non-Asia	Every 3 weeks	75	59.4	85.3%	NA	NA	78.7%	10.7%	2.8	8
Pallis AG et al 2010	[71]	2004	III	2	Non-Asia	Others	65	63.0	86.2%	18.5%	47.7%	NA	7.7%	2.6	7.7

Trial	Reference	Year of trial initiation	phase	treatment line of docetaxel	Trial region	Administration schedule of docetaxel	No of pts (Doc arm)	Age	male pts	PS2 pts	Pts with Adeno	Pts with Stage IV	ORR	PFS/TTP	OS
Segawa Y et al 2010	[72]	2005	II	2	Asia	Every 3 weeks	29	63.0	79.3%	0.0%	72.4%	79.3%	20.7%	3.7	22.9
Herbst RS et al 2010	[73]	2006	III	2	Others	Every 3 weeks	697	59.0	68.0%	0.3%	60.0%	85.0%	10.0%	4.2	9.9
Krzakowski M et al 2010	[74]	2003	III	2	Others	Every 3 weeks	277	60.0	75.3%	NA	43.6%	61.8%	5.5%	2.3	7.2
Lee DH et al 2010	[75]	2005	III	2	Asia	Every 3 weeks	79	58.0	57.0%	6.3%	69.6%	NA	7.6%	3.4	12.2
Takeda K et al 2009	[76]	2002	III	2	Asia	Every 3 weeks	65	62.0	73.8%	0.0%	61.5%	NA	6.8%	2.1	10.1
Gebbia V et al 2009	[77]	2005	III	2	Non-Asia	Weekly	47	62.0	77.0%	2.0%	45.0%	89.0%	6.4%	2.9	9.2
Jones S et al 2008	[78]	2000	II	2	Non-Asia	Every 3 weeks	38	61.5	60.5%	15.8%	NA	NA	8.0%	1.4	7.6
Paz-Ares L et al 2008	[79]	2002	III	2	Non-Asia	Every 3 weeks	422	63.0	71.6%	15.0%	NA	81.0%	12.0%	2.6	6.9
Heymach JV et al 2007	[80]	2003	II	2	Non-Asia	Every 3 weeks	41	58.0	66.0%	0.0%	48.8%	68.3%	12.0%	2.8	13.4
Chen YM et al 2006	[81]	2002	II	2,3	Asia	Weekly	64	NA	69.0%	59.4%	60.9%	90.6%	17.2%	4.2	8.4
Chen YM et al 2006	[81]	2002	II	2,3	Asia	Weekly	64	NA	66.0%	56.2%	65.6%	92.2%	10.9%	3.5	7.2

Trial	Reference	Year of trial initiation	phase	treatment line of docetaxel	Trial region	Administration schedule of docetaxel	No of pts (Doc arm)	Age	male pts	PS2 pts	Pts with Adeno	Pts with Stage IV	ORR	PFS/TTP	OS
Chen YM et al 2006	[81]	2002	II	2,3	Asia	Every 3 weeks	33	NA	70.0%	60.6%	54.5%	90.9%	6.1%	2.8	9.5
Cufer T et al 2006	[82]	2003	II	2	Non-Asia	Every 3 weeks	73	59.5	70.0%	28.8%	NA	NA	13.7%	3.4	7.1
Camps C et al 2006	[83]	2000	III	2>=	Non-Asia	Every 3 weeks	129	61	93.0%	16.3%	NA	82.9%	9.3%	2.7	6.6
Camps C et al 2006	[83]	2000	III	2>=	Non-Asia	Weekly	125	62	92.0%	16.0%	NA	84.8%	4.8%	2.9	5.4
Lai CL et al 2005	[84]	NA	II	2	Asia	Every 3 weeks	25	68	76.0%	24.0%	40.0%	68.0%	12.0%	2.6	7.8
Lai CL et al 2005	[84]	NA	II	2	Asia	Weekly	25	68	64.0%	28.0%	60.0%	76.0%	24.0%	3.0	7.3
Schuette W et al 2005	[85]	2000	III	2>=	Non-Asia	Every 3 weeks	103	63	73.8%	11.7%	30.1%	NA	12.6%	3.4	6.3
Schuette W et al 2005	[85]	2000	III	2>=	Non-Asia	Weekly	105	63	73.3%	10.5%	44.8%	NA	10.5%	3.3	9.2
Pectasides D et al 2005	[86]	NA	II	2	Non-Asia	Every 3 weeks	65	59	89.0%	12.0%	43.0%	NA	14.0%	4.8	6.4
Gervais R et al 2005	[87]	2000	II	2	Non-Asia	Every 3 weeks	62	59	80.0%	21.0%	44.0%	66.0%	4.8%	2.1	5.8
Gervais R et al	[87]	2000	II	2	Non-Asia	Weekly	63	58	81.0%	21.0%	37.0%	67.0%	3.2%	1.8	5.5

Trial	Reference	Year of trial initiation	phase	treatment line of docetaxel	Trial region	Administration schedule of docetaxel	No of pts (Doc arm)	Age	male pts	PS2 pts	Pts with Adeno	Pts with Stage IV	ORR	PFS/TTP	OS
2005															
Wachters FM et al 2005	[88]	2000	II	2	Non-Asia	Every 3 weeks	56	59	79.0%	13.0%	45.0%	75.0%	16.0%	4.2	7.4
Gridelli C et al 2004	[89]	2000	III	2	Non-Asia	Every 3 weeks	110	62	80.0%	15.0%	53.0%	81.0%	2.7%	NA	6.7
Gridelli C et al 2004	[89]	2000	III	2	Non-Asia	Weekly	110	63	86.0%	16.0%	45.0%	91.0%	5.5%	NA	5.8
Hanna N et al 2004	[90]	2001	III	2	Others	Every 3 weeks	288	57	75.3%	12.4%	49.3%	74.7%	8.8%	2.9	7.9
Quoix E et al 2004	[91]	1998	II	2	Non-Asia	Every 3 weeks	93	59	82.8%	25.8%	46.2%	62.4%	8.6%	1.5	4.7
Quoix E et al 2004	[91]	1998	II	2	Non-Asia	Others	89	59.2	82.0%	22.5%	34.8%	51.7%	7.6%	2.1	6.7
Esteban E et al 2004	[92]	1999	II	2,3	Non-Asia	Weekly	35	55	82.9%	74.0%	51.0%	NA	3.0%	2.4	6.0

Adeno: Adenocarcinoma, CP: Carboplatin and paclitaxel, pts: patients, NA: Not available, ORR: overall response rate, OS: overall survival, PFS: progression-free survival, PS: performance status